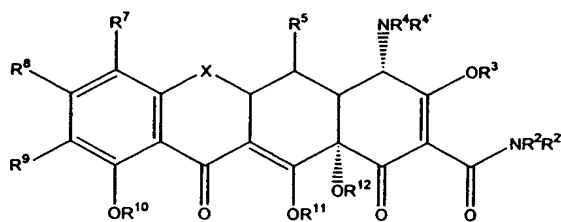


CLAIMS

1. A substituted tetracycline compound, wherein said compound is of the formula:



(I)

wherein:

X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, CR^6R^6 , S, NR^6 , or O;

R^2 is hydrogen, alkyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 and $\text{R}^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydrogen, hydroxyl, or a prodrug moiety;

R^6 , $\text{R}^{6'}$, and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, or halogen;

R^7 is hydrogen, dialkylamino, heteroaryl-amino, or $\text{NR}^{7c}\text{C}(=\text{W}')\text{WR}^{7a}$;

R^{13} is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

Y' and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

R^9 is hydrogen, $\text{NR}^{9c}\text{C}(=\text{Z}')\text{ZR}^{9a}$, or heteroaryl-amino;

Z is $\text{CR}^{9d}\text{R}^{9e}$, NR^{9b} , or O;

Z' is O or S;

R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{9d} and R^{9e} may be linked to form a ring;

W is $\text{CR}^{7d}\text{R}^{7e}$, NR^{7b} or O;

W' is O or S; and

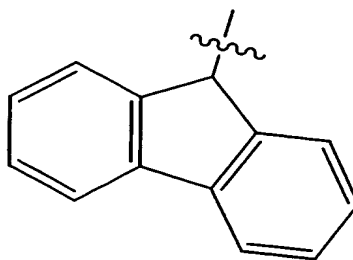
R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl,

alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{7d} and R^{7e} may be linked to form a ring;

and pharmaceutically acceptable salts thereof, provided that at least one of R⁹ is not hydrogen when R⁷ is hydrogen or dialkylamino.

- 5
2. The compound of claim 1, wherein R², R^{2'}, R³, R⁸, R¹⁰, R¹¹, and R¹² are each hydrogen.
3. The compound of claim 2, wherein R⁴ and R^{4'} are each alkyl.
- 10 4. The compound of claim 3, wherein R⁴ and R^{4'} are each methyl
5. The compound of claim 4, wherein said compound is a derivative of tetracycline, minocycline, sancycline, doxycycline, chlortetracycline, oxytetracycline, demeclocycline, or methacycline.
- 15 6. The compound of claim 4, wherein R⁵ is hydrogen.
7. The compound of claim 6, wherein X is CH₂, and R⁷ is hydrogen.
- 20 8. The compound of claim 6, wherein X is CH₂, and R⁷ is N(Me)₂.
9. The compound of claim 4, wherein R⁵ is hydroxyl or a prodrug moiety, and X is CHR⁶.
10. The compound of claim 9, wherein R⁵ is hydroxyl and R⁶ is CH₃.
- 25 11. The compound of claim 1, wherein R⁹ is NR^{9c}C(=Z')ZR^{9a}.
12. The compound of claim 11, wherein R^{9c} is hydrogen.
- 30 13. The compound of claim 11, wherein Z' is oxygen.
14. The compound of claim 11, wherein Z' is sulfur.
15. The compound of claim 13 or 14, wherein Z is NR^{9b}.
- 35 16. The compound of claim 13 or 14, wherein Z is oxygen.
17. The compound of claim 13 or 14, wherein Z is sulfur.

18. The compound of claim 13 or 14, wherein Z is CR^{9d}R^{9e}.
19. The compound of claim 11, wherein R^{9a} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaromatic, and multicyclic.
- 5 20. The compound of claim 19, wherein R^{9a} is substituted or unsubstituted alkyl.
- 10 21. The compound of claim 20, wherein R^{9a} is substituted with one or more substituents selected from the group consisting of alkoxycarbonyl, amino, arylcarbonyl, halogen, hydroxy, alkylamino, alkoxy, or aryl.
22. The compound of claim 20, wherein R^{9a} is methyl, ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl.
- 15 23. The compound of claim 21, wherein said alkyl is substituted with an aryl group.
24. The compound of claim 23, wherein said aryl group is phenyl.
- 20 25. The compound of claim 21, wherein said alkyl is substituted with one or more halogens.
26. The compound of claim 24, wherein said halogen is bromine.
27. The compound of claim 19, wherein R^{9a} is multicyclic.
- 25 28. The compound of claim 27, wherein R^{9a} is steroidyl.
29. The compound of claim 28, wherein R^{9a} is cholesterol.
- 30 30. The compound of claim 19, wherein R^{9a} is substituted or unsubstituted aryl.
31. The compound of claim 30, wherein said substituted or unsubstituted aryl is naphthyl.
32. The compound of claim 30, wherein said substituted or unsubstituted aryl is of the formula:



33. The compound of claim 30, wherein said substituted or unsubstituted aryl is phenyl.
- 5 34. The compound of claim 33, wherein said aryl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, amido, halogen, nitro, azo, alkyl sulfonyl, and arylsulfonyl.
- 10 35. The compound of claim 34, wherein said substituent is alkyl.
36. The compound of claim 35, wherein said alkyl is unsubstituted.
37. The compound of claim 35, wherein said alkyl is methyl.
- 15 38. The compound of claim 35, wherein said alkyl is substituted with one or more halogens.
39. The compound of claim 34, wherein said substituent is methoxy.
- 20 40. The compound of claim 34, wherein said substituent is selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, and amido.
41. The compound of claim 1, wherein R^9 is heteroaryl-amino.
- 25 42. The compound of claim 41, wherein said heteroaryl is substituted or unsubstituted thioazolyl.
43. The compound of claim 42, wherein said heteroaryl is substituted thioazolyl.
- 30 44. The compound of claim 43, wherein said thiazolyl is substituted with a substituted or unsubstituted aryl.
45. The compound of claim 46, wherein said aryl is phenyl.

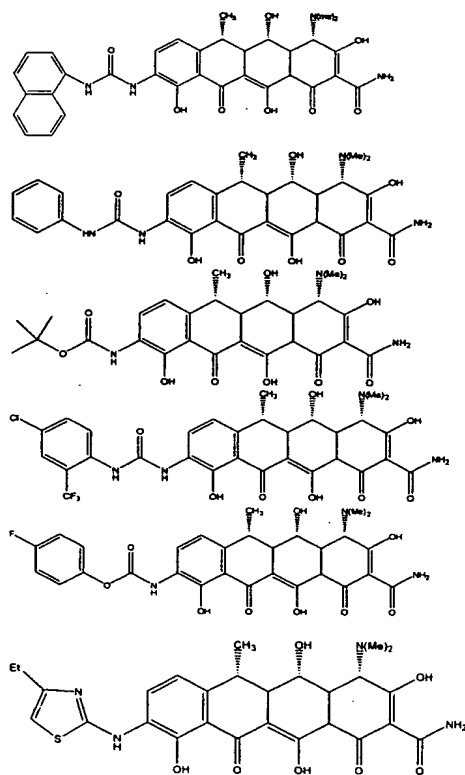
46. The compound of claim 44, wherein said aryl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, amido, trifluoromethyl, halogen, nitro, azo, alkyl sulfonyl, and arylsulfonyl.
47. The compound of claim 46, wherein said substituent is nitro.
48. The compound of claim 46, wherein said substituent is alkyl.
49. The compound of claim 48, wherein said alkyl substituent is methyl.
50. The compound of claim 46, wherein said substituent is selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy, and amido.
51. The compound of claim 50, wherein said substituent is alkoxycarbonyl.
52. The compound of claim 51, wherein said substituent is ethoxycarbonyl.
53. The compound of claim 1, wherein said compound is selected from the group consisting of: Doxycycline 9-carbamic acid 9H-fluoren-9-ylmethyl ester; (9-(Naphthyn-1-yl) doxycycline urea; 9-(3-Methyl-1-butyl) doxycycline urea; 9-Phenyl doxycycline urea; 9-t-Butyl doxycycline urea; Fmoc 9-amino doxycycline; 9-(4'-Chloro-2'-trifluoromethylphenyl) doxycycline urea; 9-(4'-Fluorophenyl) doxycycline carbamate; 9-(4'-Methoxyphenyl) doxycycline carbamate; 9-BOC amino doxycycline; 9-(Phenylthiazolyl) amino doxycycline; 9-(Ethylthiazolyl) amino doxycycline; (4-Fluorophenylthiazolyl) amino doxycycline; 9-(4'-Methoxyphenylthiazolyl) amino doxycycline; 9-(3'-Nitrophenylthiazolyl) amino doxycycline; 9-(4'-Methyl, 5'-phenylthiazolyl) amino doxycycline; 9-Neopentyl minocycline carbamate; 9-(Phenylthiazolyl) amino sancycline;

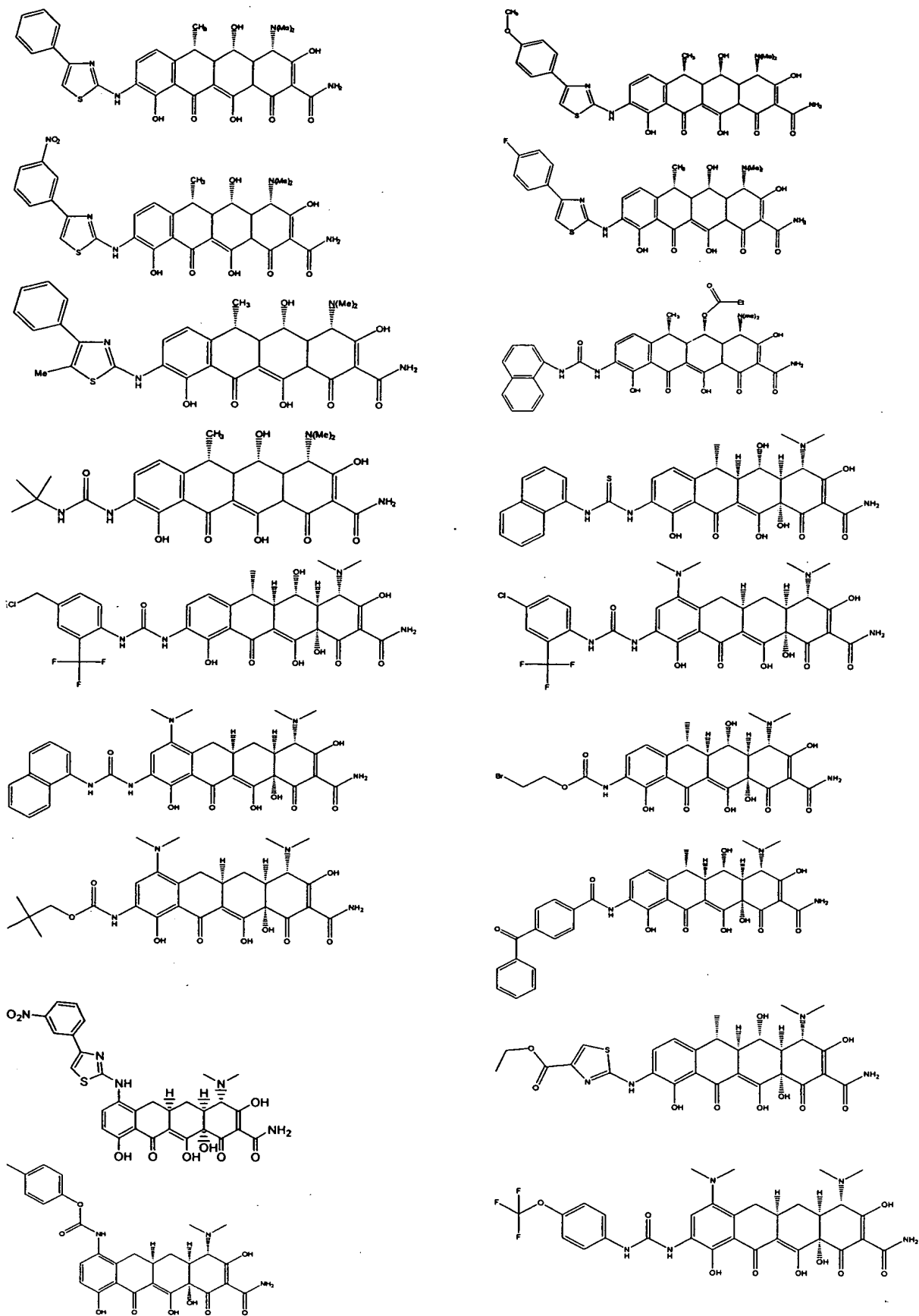
- 9-(Adamantylthiazolyl) amino doxycycline;
- 9-(Naphthyn-1-yl urea) Doxycycline 5-propanoic acid ester;
- Doxycycline 9-Thiocarbamic acid 9*H*-fluoren-9-ylmethyl ester;
- (9-(Naphthyn-1-yl) doxycycline thiourea;
- 5 9-(3-methyl-1-butyl) doxycycline thiourea;
- 9-Phenyl doxycycline thiourea;
- 9-*t*-Butyl doxycycline thiourea;
- 9-(4'-Chloro-2'-trifluoromethylphenyl) doxycycline thiourea;
- 9-(4'-Fluorophenyl) doxycycline thiocarbamate;
- 10 9-(4-Methoxyphenyl) doxycycline thiocarbamate;
- 9-Neopentyl minocycline thiocarbamate;
- 9-(Naphthyn-1-yl) doxycycline thiourea 5-propanoic acid ester;
- Minocycline 9-carbamic acid 9*H*-fluoren-9-ylmethyl ester;
- (9-(Naphthyn-1-yl) minocycline urea;
- 15 9-(3-Methyl-1-butyl) minocycline urea;
- 9-Phenyl doxycycline urea;
- 9-*t*-Butyl minocycline urea;
- FMOC 9-amino minocycline;
- 9-(4'-Chloro-2'-trifluoromethylphenyl) minocycline urea;
- 20 9-(4'-Fluorophenyl) minocycline carbamate;
- 9-(4'-Methoxyphenyl) minocycline carbamate;
- 9-BOC amino minocycline;
- 9-(Phenylthiazolyl) amino minocycline;
- 9-(Ethylthiazolyl) amino minocycline;
- 25 (4'-Fluorophenylthiazolyl) amino minocycline;
- 9-(4'-Methoxyphenylthiazolyl) amino minocycline;
- 9-9-(3'-Nitrophenylthiazolyl) amino minocycline;
- 9-(4'-Methyl, 5'-phenylthiazolyl) amino doxycycline;
- 9-Neopentyl doxycycline carbamate;

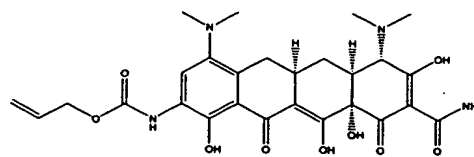
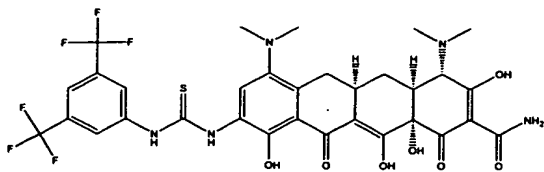
- 30
- 54. The compound of claim 1, wherein said compound is selected from the group consisting of: 9-(Phenylthiazolyl) amino minocycline;
- 9-(Adamantylthiazolyl) amino minocycline;
- Minocycline 9-thiocarbamic acid 9*H*-fluoren-9-ylmethyl ester;
- 35 (9-(Naphthyn-1-yl) minocycline thiourea;
- 9-(3'-Methyl-1-butyl) minocycline thiourea;
- 9-Phenyl minocycline thiourea;
- 9-*t*-Butyl minocycline thiourea;

- 4

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56. The compound of claim 1, wherein R^7 is $NR^{7c}C(=W')WR^{7a}$.

57. The compound of claim 56, wherein R^9 is hydrogen.

58. The compound of claim 57, wherein R^{7c} is hydrogen.

59. The compound of claim 57, wherein W' is oxygen.

60. The compound of claim 57, wherein W' is sulfur

61. The compound of claims 59 or 60, wherein W is NR^{7b} .

62. The compound of claims 59 or 60, wherein W is oxygen.

63. The compound of claim 57, wherein R^{7a} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaromatic, and multicyclic.

64. The compound of claim 63, wherein R^{7a} is substituted or unsubstituted alkyl.

65. The compound of claim 64, wherein said alkyl is substituted with an aryl group.

66. The compound of claim 63, wherein said substituted or unsubstituted aryl is phenyl.

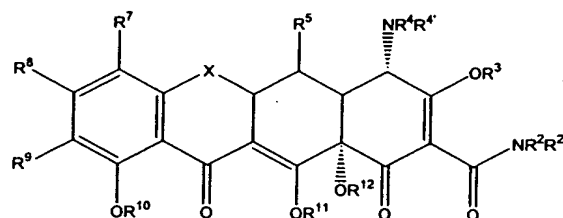
67. The compound of claim 66, wherein said aryl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amido, halogen, nitro, azo, alkyl sulfonyl, and arylsulfonyl.

68. The compound of claim 67, wherein said substituent is alkyl, alkoxy, or nitro.

69. The compound of claim 1, wherein R⁷ is heteroaryl-amino.
70. The compound of claim 69, wherein R⁹ is hydrogen.
- 5 71. The compound of claim 70, wherein said heteroaryl is substituted or unsubstituted thioazolyl.
72. The compound of claim 71, wherein said thiazolyl is substituted with a substituted or unsubstituted aryl.
- 10 73. The compound of claim 72, wherein said aryl is phenyl.
74. The compound of claim 73, wherein said aryl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, amido, trifluoromethyl, halogen, nitro, azo, alkyl sulfonyl, and arylsulfonyl.
- 15 75. The compound of claim 74, wherein said substituent is nitro.
- 20 76. The compound of claim 1, wherein said compound is selected from the group consisting of: Doxycycline 7-carbamic acid 7*H*-fluoren-7-ylmethyl ester; 7-(Naphthyn-1-yl) doxycycline urea; 7-(3-Methyl-1-butyl) doxycycline urea; 7-Phenyl doxycycline urea; 25 7-*t*-Butyl doxycycline urea; 7-Fmoc amino doxycycline; 7-(4'-Chloro-2-trifluoromethylphenyl) doxycycline urea; 7-(4'-Fluorophenyl) doxycycline carbamate; 7-(4'-Methoxyphenyl) doxycycline carbamate; 30 7-BOC amino doxycycline; 7-(3'Phenylthiazolyl) amino doxycycline; 7-(3'-Ethylthiazolyl) amino doxycycline; 7-(4''-Fluorophenylthiazolyl) amino doxycycline; 7-(4''-Methoxyphenylthiazolyl) amino doxycycline; 35 7-(Phenylthiazolylamino)-sancycline; 7-(3'-Nitrophenylthiazolyl) amino doxycycline; 7-(4'-Methyl, 5'-phenylthiazolyl) amino doxycycline; 7-(Adamantylthiazolyl) amino doxycycline;

- Doxycycline 7-thiocarbamic acid 7*H*-fluoren-7-ylmethyl ester;
 7-(Naphthyn-1-yl) doxycycline thiourea;
 7-(3-Methyl-1-butyl) doxycycline thiourea;
 7-Phenyl amino doxycycline thiourea;
 5 7-*t*-butyl amino doxycycline thiourea;
 7-(4'-Chloro-2'-trifluoromethylphenyl) doxycycline thiourea;
 7-(4'-Fluorophenyl) doxycycline thiocarbamate;
 7-(4'-Methoxyphenyl) doxycycline thiocarbamate;
 7-(Naphthyn-1-yl) doxycycline urea 5-propanoic acid ester;
 10 7-(Naphthyn-1-yl) doxycycline thiourea 5-propanoic acid ester, and pharmaceutically acceptable salts thereof.

77. A method for treating a tetracycline responsive state in a mammal, comprising administering to said mammal a substituted tetracycline compound of formula (I):



(I)

wherein

- X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, CR^6R^6 , S, NR^6 , or O;
 R^2 is hydrogen, alkyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl,
 20 alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
 R^4 and $\text{R}^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a
 prodrug moiety;
 $\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;
 25 R^5 is hydrogen, hydroxyl, or a prodrug moiety;
 R^6 , $\text{R}^{6'}$, and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl,
 alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, or halogen;
 R^7 is hydrogen, dialkylamino, heteroaryl-amino, or $\text{NR}^{7c}\text{C}(=\text{W}')\text{WR}^{7a}$;
 R^{13} is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio;
 30 alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;
 Y' and Y are each independently hydrogen; halogen; hydroxyl; cyano,
 sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl;
 alkylamino; or an arylalkyl;
 R^9 is hydrogen, $\text{NR}^{9c}\text{C}(=\text{Z}')\text{ZR}^{9a}$, or heteroaryl-amino;

Z is CR^{9d}R^{9e}, NR^{9b}, or O;

Z' is O or S;

R^{9a}, R^{9b}, R^{9c}, R^{9d}, and R^{9e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{9d} and R^{9e} may be linked to form a ring;

W is CR^{7d}R^{7e}, NR^{7b} or O;

W' is O or S; and

R^{7a}, R^{7b}, R^{7c}, R^{7d}, and R^{7e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{7d} and R^{7e} may be linked to form a ring;

and pharmaceutically acceptable salts thereof, provided that when R⁹ is not hydrogen when R⁷ is hydrogen or dialkylamino.

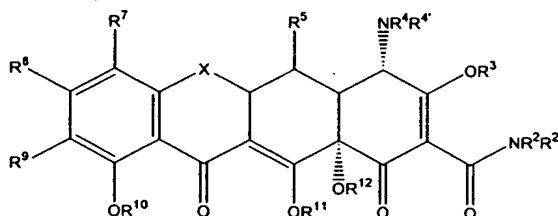
78. The method of claim 77, wherein said tetracycline responsive state is a bacterial infection.

79. The method of claim 78, wherein said bacterial infection is associated with *E. coli*, *S. aureus*, *E. faecalis*, or *E. hirae*.

80. The method of claim 78, wherein said bacterial infection is resistant to unsubstituted tetracycline compounds.

81. The method of claim 77, wherein said tetracycline compound is administered with a pharmaceutically acceptable carrier.

82. A pharmaceutical composition comprising a therapeutically effective amount of a substituted tetracycline compound and a pharmaceutically acceptable carrier, wherein said substituted tetracycline is of the formula:



(I)

wherein:

X is CHC(R¹³Y'Y), CR⁶R⁶, S, NR⁶, or O;

R^2 is hydrogen, alkyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydrogen, hydroxyl, or a prodrug moiety;

R^6 , $R^{6'}$, and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, or halogen;

R^7 is hydrogen, dialkylamino, heteroaryl-amino, or $NR^{7c}C(=W')WR^{7a}$;

R^{13} is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

Y' and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

R^9 is hydrogen, $NR^{9c}C(=Z')ZR^{9a}$, or heteroaryl-amino;

Z is $CR^{9d}R^{9e}$, NR^{9b} , or O;

Z' is O or S;

R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{9d} and R^{9e} may be linked to form a ring;

W is $CR^{7d}R^{7e}$, NR^{7b} or O;

W' is O or S; and

R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety, and R^{7d} and R^{7e} may be linked to form a ring;

and pharmaceutically acceptable salts thereof, provided that R^9 is not hydrogen, when R^7 is dialkylamino or hydrogen.

83. The pharmaceutical composition of claim 82, wherein said therapeutically effective amount is effective for treatment or prevention of a bacterial infection.

84. A method for synthesizing a 7- or 9- substituted tetracycline compound, comprising:
contacting a tetracycline compound with a nitrating agent, under conditions such that a nitro tetracycline compound is formed;

contacting the nitro tetracycline compound with a hydrogenating agent, under conditions such that an amino tetracycline compound is formed; and

contacting the amino tetracycline compound with an amino reactive substrate, such that a 9- or 7- substituted tetracycline compound is formed.

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85. The method of claim 84, wherein said substituted tetracycline compound is 9-substituted.

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86. The method of claim 84, wherein said substituted tetracycline compound is 7-substituted.

87. The method of claim 84, wherein the nitrating agent is NaNO_2 .

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88. The method of claim 84, wherein the nitrating agent is contacted with the tetracycline compound under acidic conditions.

89. The method of claim 84, wherein said hydrogenating agent is hydrogen gas.

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90. The method of claim 89, wherein said hydrogenating agent further comprises a transition metal catalyst.

91. The method of claim 90, wherein said catalyst is platinum.

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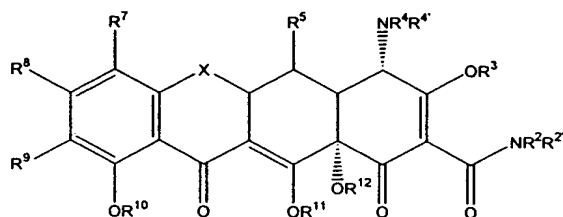
92. The method of claim 84, wherein said amino reactive compound is an isocyanate.

93. The method of claim 84, wherein said amino reactive compound is isothiocyanate.

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94. The method of claim 84, wherein said amino reactive compound is an unsubstituted or substituted chloroformate.

95. A method for synthesizing a 7- or 9- substituted tetracycline compound of formula (I) comprising contacting a reactive intermediate with appropriate reagents under appropriate conditions, such that a substituted tetracycline compound is formed, wherein formula (I) is:



(I)

wherein:

X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, $\text{CR}^{6'}\text{R}^6$, S, NR^6 , or O;

R^2 is hydrogen, alkyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 and $\text{R}^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydrogen, hydroxyl, or a prodrug moiety;

R^6 , $\text{R}^{6'}$, and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, or halogen;

R^7 is hydrogen, dialkylamino, heteroaryl-amino, or $\text{NR}^{7c}\text{C}(=\text{W}')\text{WR}^{7a}$;

R^{13} is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

Y' and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;

R^9 is hydrogen, $\text{NR}^{9c}\text{C}(=\text{Z}')\text{ZR}^{9a}$, or heteroaryl-amino;

Z is $\text{CR}^{9d}\text{R}^{9e}$, NR^{9b} , or O;

Z' is O or S;

R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety;

W is $\text{CR}^{7d}\text{R}^{7e}$, NR^{7b} or O;

W' is O or S; and

R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or a prodrug moiety;

and pharmaceutically acceptable salts thereof, provided that R^9 is not hydrogen when R^7 is dialkylamino or hydrogen.

96. The method of claim 95, wherein said reactive intermediate is a 7- or 9- diazonium salt.

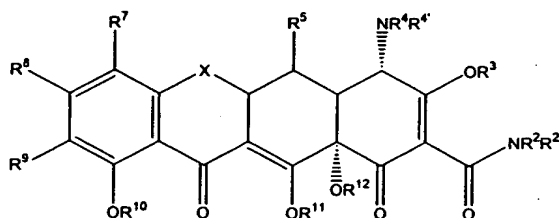
97. The method of claim 95, wherein said reactive intermediate is a 7- or 9- nitro compound.

98. The method of claim 95, wherein said reactive intermediate is a 7- or 9- thiourea.

99. The method of claim 95, wherein said reactive intermediate is a 7- or 9- thiocarboxamide.

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100. A reactive intermediate, wherein said reactive intermediate is of the formula:



(I)

wherein:

- 10 X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, CHR^6 , S, NR^6 , or O;
 R^2 is hydrogen, alkyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
 R^4 and $\text{R}^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a
15 prodrug moiety;
 $\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;
 R^5 is hydrogen, hydroxyl, or a prodrug moiety;
 R^6 and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
20 R^{13} is hydrogen, hydroxy, alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;
 Y' and Y are each independently hydrogen; halogen; hydroxyl; cyano, sulfhydryl; amino; alkyl; alkenyl; alkynyl; alkoxy; alkylthio; alkylsulfinyl; alkylsulfonyl; alkylamino; or an arylalkyl;
25 R^9 is hydrogen, thiourea, diazonium salt, thiocarboxamide, or nitro;
 R^7 is hydrogen, dialkylamino, thiourea, diazonium salt, thiocarboxamide, or nitro; and pharmaceutically acceptable salts thereof, provided that both R^9 is not hydrogen when R^7 is dialkylamino or hydrogen.

30 101. The reactive intermediate of claim 100, wherein R^7 is H, and R^9 is thiourea, diazonium salt, thiocarboxamide, or nitro moiety.

102. The reactive intermediate of claim 100, wherein R^9 is H, and R^7 is thiourea, diazonium salt, thiocarboxamide, or nitro moiety.